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ACTINIDE-SPECIFIC SEQUESTERING AGENTS AND DECONTAMINATION APPLICATIONS

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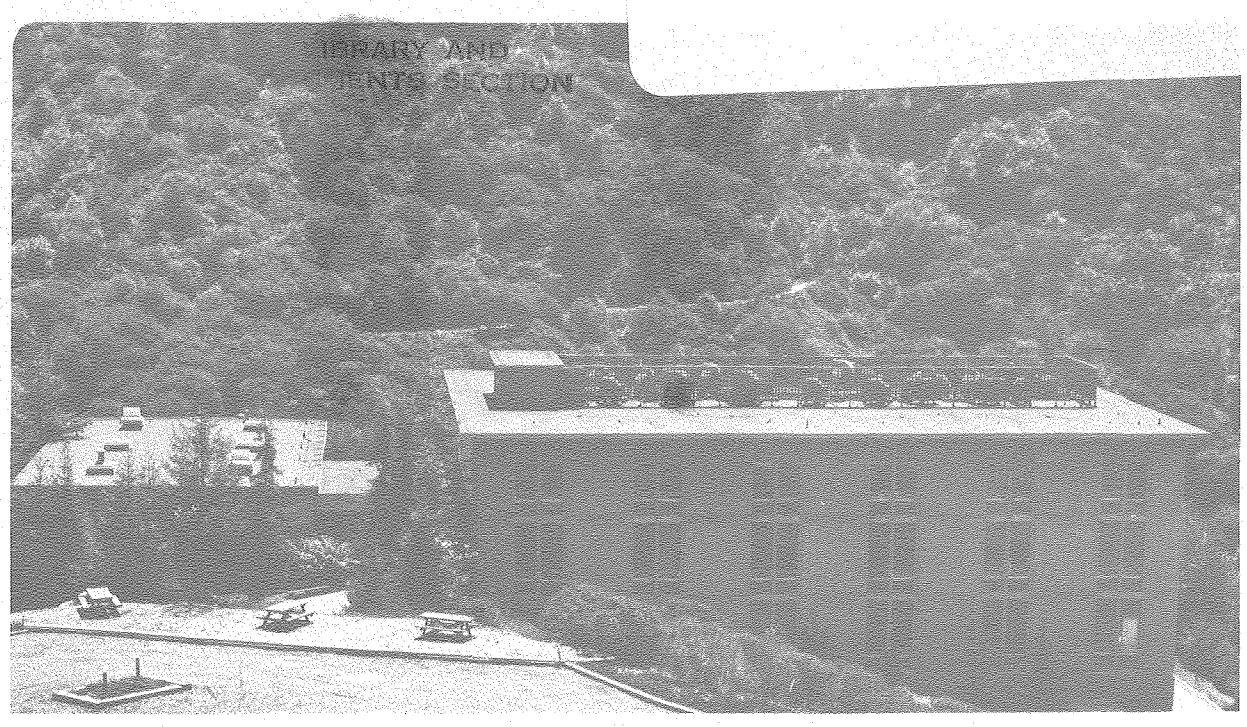

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Actinide-Specific Sequestering Agents and Decontamination Applications

by

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I. Introduction

With the commercial development of nuclear reactors, the actinides have become important industrial elements. A major concern of the nuclear industry is the biological hazard associated with nuclear fuels and their wastes (1,2). As seen in Table 1, the acute chemical toxicity of tetravalent actinides, as exemplified by Th(IV), is similar to Cr(III) or Al(III). However, the acute toxicity of ^{239}Pu(IV) is similar to strychnine, which is much more toxic than any of the non-radioactive metals such as mercury. Although the more radioactive isotopes of the transuranium elements are more acutely toxic by weight than plutonium, the acute toxicities of ^{239}Pu, ^{241}Am, and ^{244}Cm are nearly identical in radiation dose, ~100 μCi/kg in rodents (6). Thus, the extreme acute toxicity of ^{239}Pu is attributed to its high specific activity of alpha emission (6-8).

Unlike organic poisons, biological systems are unable to detoxify metal ions by metabolic degradation. Instead, unwanted metal ions are excreted or immobilized (9). Unfortunately, only a small portion of absorbed tetra- or trivalent actinide is eliminated from a mammalian body during its lifetime. The remaining actinide is distributed throughout the body but is especially found fixed in the liver and in the skeleton (6,8,10-13). While the ability of some metals to do damage is greatly reduced by immobilization, local high concentrations of radioactivity are produced by immobilized actinides - thereby increasing the locally absorbed radiation dose and the carcinogenic potential. Thus the long-term, chronic toxicity is much greater than the immediate, acute toxicity.

Primarily through the induction of bone cancer or tumors of blood forming tissue, very low doses of ^{239}Pu significantly shorten the life span of laboratory animals (5,6,8,14-17). While mice suffered no ill effects from plutonium doses less than 1/1000 of the acutely toxic dose (~1 μg/kg) (17), a dose of 0.26 μg/kg given to dogs increased the incidence of bone cancer from 1/10,000 to 1/3 and decreased their lifespan 14% (17). Lung cancer formed in all dogs that inhaled ~1 μg/kg of plutonium oxide, but their lifespan was not significantly shortened (18). Removal of very small amounts of actinides from the body is therefore an essential component of treatment for actinide contamination, particularly Pu(IV).

II. Biochemistry of Plutonium

While not the most toxic, plutonium is the most likely transuranium element to be encountered. In addition to the several kilograms of naturally occuring plutonium, about 5,000 kg of plutonium has been released during nuclear weapons testing, accidental destruction of nuclear devices, and nuclear fuels reprocessing (19-21). Fortunately, the viable routes of plutonium contamination are limited to direct physical transport, since the inability of plutonium to cross physiological membranes prevents its concentration in the food chain (20-22). The concentration of plutonium in plants is 10^{-4} to 10^{-6} of the surrounding soil (23). Further, only 0.03% of ingested Pu(IV) citrate is absorbed by the gastrointestinal tract of mammals, while much smaller amounts of less stable chelates, simple salts, or insoluble compounds of plutonium are absorbed (10,11,13,24). Similarly, insignificant amounts of plutonium are absorbed through intact skin during long exposures to highly

acidic plutonium solutions (25). Thus human contamination by environmental plutonium would seem to be limited to the direct ingestion or inhalation of plutonium resuspended from soil. However, there continues to be concern that naturally-occuring chelating agents might complex plutonium sufficiently strongly to change this view. Occupationally, plutonium has gained admittance to humans principally through inhalation and wounds (26).

The biological behavior of plutonium is dependent on the chemical form. Insoluble compounds of plutonium, such as oxides, fluorides, and hydroxides, largely remain in the lung or at the site of an intramuscular wound. Particles of these insoluble compounds may be slowly transported to the lymph nodes, and a small portion may react with biological ligands to form soluble complexes that are transported by the circulatory system (10,27-29). Extremely small particles of PuO_2 when inhaled as aerosols are rapidly absorbed from the lung and enter the circulation as low molecular-weight complexes (30). Plutonium chelates are quickly and completely absorbed from the site of entry, but metabolically inert complexes, such as Pu-DTPA, are rapidly and nearly quantitatively excreted. Complexes of metabolizable ligands, such as citrate and ascorbate, are not excreted, but give up their plutonium to plasma proteins. Other compounds of plutonium such as hydrolyzable chelates and simple salts are partially absorbed into the circulation. Much larger amounts of Pu(III) and Pu(VI), which hydrolyze less readily than Pu(IV), are absorbed. The remainder hydrolyzes to form an insoluble deposit, which behaves as described above (10,11,27,31).

Particularly in the case of plutonium hydroxide, the amount of plutonium solublized from an internal deposit by biological ligands depends upon the oxidation state of the deposited plutonium. The charge to ionic-radius ratio and the tendency towards hydrolysis decreases in the order (32,33);

$$Pu^{4+} > PuO_2^{2+} > Pu^{3+} > PuO_2^{+}.$$

In the absence of chelating agents, hydrolysis of Pu(IV), a strong lewis acid, occurs rapidly at low pH. Ultimately, insoluble colloids and polymers of $Pu(OH)_4$ are formed. A 4×10^{-3} M solution of Pu(IV) at pH = 1 was 40% polymerized in 30 minutes (34), but pseudocolloids of $Pu(OH)_4$ did not form in a 6.8×10^{-8} M solution of Pu(IV) until the pH was raised to 2.8 and polymerization was not complete below pH = 7.5 (35). The redissolution of Pu(IV) hydroxides proceeds slowly, even in the presence of chelating agents (36,37). Because of their decreased acidity, Pu(III) and Pu(VI) hydrolyze less readily than Pu(IV). Hydrolysis of a 10^{-9} M solution of Am(III) or Cm(III) begins at pH = 4.5, and colloidal species form near pH = 7 (38). The solubility product of $Pu(OH)_3$ (2×10^{-20}) is much greater than that of $Pu(OH)_4$ (7×10^{-56}) (39). Thus, the amount and the rate of dissolution of an insoluble plutonium deposit increases in the order; Pu(III) > Pu(VI) > Pu(IV).

While the hydrolytic behavior of the oxidation state determines the amount and the rate of plutonium absorbed from the lungs or from a wound, the tissue distribution of the absorbed Pu was indistinguishable when Pu(III), Pu(IV), or Pu(VI) was administered to rats (40). Thus, once plutonium enters the circulation its behavior is independent of its original oxidation state. Biologically plutonium behaves like thorium

(41,42), which is stable in solution only as a tetravalent ion. While the biological behavior of Am(III) and Cm(III) is similar to plutonium, there are significant differences in the binding to endogenous ligands, biological transport, distribution, and rate of elimination (6,10,11,43). In contrast to tri- and tetravalent actinides, the oxocations, as exemplified by the uranyl ion, are rapidly absorbed from lungs and wounds, and the majority of the absorbed uranium is rapidly excreted as an uranyl-bicarbonate complex (44-46).

In aqueous solutions each of the oxidation states of plutonium from III to VI coexist in equilibrium, and depending on the conditions and relative concentrations of the oxidation states disportionation may occur. The redox behavior of ^{239}Pu is further complicated by its high specific activity of alpha radiation. The radiolytic decomposition of water produces oxidants (HO and HO_2 radicals, H_2O_2) and reductants (H_2O_2, H radicals), which may oxidize or reduce plutonium, depending on the relative proportions of the different valency states initially present (47). However, Pu(III) is oxidized to Pu(IV) by water at neutral pH and Pu(III) hydroxide is rapidly oxidized by air to Pu(IV) hydroxide; while Pu(VI) is reduced to Pu(IV) by Fe(II) (33). Further, the complexing ability of plutonium decreases in the order (48-50);

$$Pu^{4+} > Pu^{3+} \approx PuO_2^{2+} > PuO_2^{+}.$$

Although there is no direct measurement of the oxidation state of plutonium in biological fluids, redox potentials, complexation and hydrolysis strongly favor Pu(IV) as the dominant specie.

Plutonium which is absorbed into the circulatory system of mammals, either by injection of a metabolizable complex or by solubilization of

plutonium deposited in a wound or in a lung, is quickly and strongly bound to transferrin, the iron transport protein found in the plasma of mammals. Small amounts of plutonium are associated with other macroglobulins or complexed with low molecular-weight substances such as citrate, sugars and peptides (32,43,51-54). While the exact nature of the binding of Pu(IV) to transferrin is unknown, it appears to be bound by the same sites that bind iron. As with iron, bicarbonate is required in the formation of the Pu-transferrin complex (55). Plutonium is displaced by Fe(III) and does not bind to iron saturated transferrin (51,55). Titrimetric experiments show that transferrin specifically binds Th(IV) at the same sites as Fe(III) (56). Further, the half-life for the removal of plutonium from circulation nearly equals that of iron, such that after 1 hour 70% of the injected plutonium is still in circulation. In contrast, 86% of the injected Am(III) or Cm(III) is removed from the blood within one minute. Thus, the trivalent actinides are not complexed by transferrin, but are weakly associated among various plasma proteins (53,54). The complexation of plutonium by transferrin effectively prevents its excretion, but small amounts are excreted as the citrate complex in the urine (51).

Colloids and particles of insoluble plutonium compounds which enter the circulatory system are not complexed by transferrin, but accumulate primarily in the liver. Small amounts are also found in the spleen and bone marrow. These organs have a high concentration of reticuloendothelial cells, which act as filters to consume rapidly any colloidal particles (54,57-59). While the extent of hydrolysis depends on the oxidation state, a portion of an intravenously injected, hydrolyzable salt of plutonium, such as the nitrate or the chloride, forms insoluble

colloids of hydrolyzed plutonium that are removed mainly by the liver. The remainder is complexed and transported by transferrin (10,54).

Circulating as the Pu-transferrin complex, plutonium is initially distributed throughout the body, but is eventually deposited as single atoms primarily on bone surfaces close to the marrow and the circulatory system (10). Initially the plutonium appears to bind to the glycoproteins present in the organic matrix of bone. These proteins contain many free carboxyl groups and bind plutonium stronger than a 30-fold excess of bone mineral or any other protein investigated, including transferrin (32,51,60). The carboxyl groups of the proteins appear to be important in binding Pu(IV), but not Am(III) or Cm(III), which are less strongly bound. The trivalent actinides are uniformly distributed on all bone surfaces and tend to deposit on bone mineral to a greater extent than plutonium (10,43).

Once deposited on bone, plutonium is not released until the bone is physically destroyed. It may become buried under a new layer of mineral or may be taken up by special cells that digest foreign materials. As these cells die, the plutonium accumulates in immobilized deposits of hemosiderin, an insoluble iron storage protein that contains a large core of polymeric iron hydroxides and phosphates. These deposits are located close to the bone surfaces in the reticuloendothelial cells of the bone marrow (10).

In addition to deposition on bones, smaller, but significant amounts of circulating plutonium is deposited in the liver (10). Initially the plutonium is distributed throughout the liver, where it is bound principally in the cytosol of cells to an unidentified protein

that has the chromatographic characteristics of a γ-globulin (61). Within several days, the plutonium becomes associated with subcellular structures, where it is primarily bound to ferritin, a soluble iron-storage protein. Small amounts of plutonium are associated with other proteins located on the subcellular structures such as glucose-6-phosphatase, cytochrome-c-oxidase, aryl-sulphatase, acid-phosphatase and unknown glycoproteins (51,62). In an attempt to minimize their toxic effects, other toxic metals are similarly immobilized on subcellular structures (43).

As the liver cells die, the plutonium accumulates in the hemosiderin of the reticulioendothelial cells (10). As in the bone marrow and the liver, plutonium in the spleen and the adrenal glands is also localized with hemosiderin (43,63). Incorporation of plutonium into hemosiderin or the mineral matrix of bone is not permanent, but the mechanisms of release are not known. However, it is more probable that released plutonium will be complexed by transferrin and redeposited instead of excreted (10). In fact, the human iron transport system is so efficient in preventing plutonium excretion that only 20-30% of the plutonium injected into humans was excreted during 27.4 years (12). In view of the role of iron transport and storage proteins in the mammalian metabolism of plutonium, it is not surprising that the highest uptake of plutonium occurs in plants grown in iron deficient conditions (53).

III. Therapeutic Removal of Plutonium

1. Colloidal Scavenging Agents

One of the earliest attempts to remove plutonium from mammals was based on the premise that an innocuous metal ion with metabolic

properties similar to plutonium would displace plutonium from body tissues - as occurs on an ion exchange resin. Because of its low toxicity in rodents and its rapid elimination from the body, zirconium was the most promising of the metals tested (64). The details of the biological testing have been summarized in previous reviews (13,65,66). Typically, 50-60% of the injected plutonium was rapidly excreted in the urine of rats which received an injection of 40-50 mg of zirconium in the form of zirconyl citrate within one hour of the plutonium administration, while only 1-2% of the injected plutonium was excreted by untreated rats (66-69). Prompt treatment with zirconyl citrate was reported to remove up to 90% of the injected plutonium from dogs (70). However, the amount of excreted plutonium dropped rapidly as the time between treatment and plutonium administration increased. When two hours elapsed between plutonium and zirconyl citrate injections, only 10% of the injected plutonium was excreted (64). Treatment with zirconyl citrate $2\frac{1}{2}$ years after the plutonium injection in dogs increased the excretion of plutonium 10-15 fold, but the initial level of excretion was so low that the additional amount of plutonium removed was negligible (69).

These results indicate that zirconyl citrate is effective only in the removal of plutonium from the circulation system and not from body tissues. This is consistent with the reduction of plutonium in the blood of treated rats to 50% of the control value after five minutes and to 10% after one hour (66,71). The actual mechanism of plutonium removal probably involves the hydrolysis of zirconium to form colloidal aggregates of zirconium hydroxides and phosphates. Other hydrolyzable metals, such as plutonium and thorium, either coprecipitate with the zirconium or are absorbed by the colloids, which act as carriers

(65,66). In an analogous manner, the high affinity of plutonium(IV) for colloidal iron hydroxide probably explains the strong association of plutonium(IV) to ferritin and to iron storage pigments such as hemosiderin (63). As predicted by this mechanism, manganese, iron, titanium, aluminum and thorium, metals which hydrolyze under physiological conditions, also serve as carriers (72). However, not all of these metals promoted plutonium excretion. The larger colloids do not pass through the kidneys, but are filtered from the blood by organs such as the liver, spleen and bone marrow. Thus thorium and aluminium, which hydrolyze to form large polymers, prevent the deposition of plutonium on the skeleton, but cause an increase in the amount of plutonium deposited in the liver (72).

Prompt administration of polymeric phosphates have also been successful in increasing plutonium excretion from laboratory animals (73). Hexametaphosphate was found to reduce bone absorption of plutonium by a factor of three, but this was accompanied by an increase in the liver burden of plutonium (74). Thus, it seems likely that plutonium and polymeric phosphates form colloids that behave similarly to those formed with zirconium, except that the phosphates are more toxic. Alternatively, phosphate groups may bind to bone. Pretreatment with ethane-1-hydroxy-1,1-diphosphoric acid or dichloromethylenediphosphoric acid inhibited the mineralization and growth of bone as well as the skeletal uptake of plutonium (75).

2. Chelating Agents

The most promising approach to the removal of incorporated plutonium uses chelating agents to form soluble, excretable complexes of

plutonium. Sodium citrate was the first complexing agent to be tested for plutonium removal (76). Although plutonium is naturally excreted as the citrate complex (77), the rapid metabolism of sodium citrate and its complexes decreases its effectiveness as a chelating agent. Administration of sodium citrate within two hours after the injection of plutonium increased urinary excretion several fold, but the increase was not sufficient to be of practical importance (64). However, the excretion of thorium was increased from the control value of 28% to 47% of the injected thorium by treatment with sodium citrate 30 minutes after the injection of thorium (78).

The limited success with sodium citrate led to the trial and error testing of other chelating agents. Despite the fact that hard Lewis acids such as plutonium do not bind strongly to sulfur ligands, the success of 2,3-dimercapto-1-propanol, BAL, as an efficient chelator for arsenic (79) led to testing its ability to remove actinides. As expected on a chemical basis, excretion of plutonium was not enhanced by treatment with BAL, methionine, or cysteine (67,80). Several other sulfur containing compounds were also found to have a negligible effect on the excretion of lanthanides (81). Similar results were obtained for biologically occurring complexing agents, such as ascorbic acid, nicotinic acid and creatine, as well as for nitrilotriacetic acid (NTA), and picolinic acid. However, since 70% of the yttrium administered simultaneously with therapeutic doses of ethylenediaminetetraacetic acid (EDTA) was excreted from rats in 24 hours (81), the use of EDTA was suggested for plutonium removal. Rats receiving plutonium followed by EDTA in the first 24 hours excreted ten times the plutonium of the control group (82). Another study showed that an injection of EDTA immediately

following the plutonium increased the urinary excretion in rats from the control value of 6% to 51% of the injected plutonium (83). As with zirconium, a large dose of EDTA administered 30 days after the plutonium did not significantly decrease the body burden of plutonium in rats (84). Other authors have reviewed in more detail the removal of plutonium from mammals, including humans, using EDTA (6,13,65).

Further selection of chelating agents for plutonium removal has involved the ratio of the stability constants of the plutonium and calcium complexes formed with the chelating agent. Schubert suggested that since the concentration of serum calcium is much greater than that of other metals, any chelating agent capable of complexing calcium would exist as the calcium chelate in the circulation system. Thus, similar increases in plutonium removal would be achieved by either decreasing the chelating agent's affinity for calcium or by increasing its affinity for plutonium (65). Other endogenous metals become significant only when they are complexed much more strongly than calcium. The use of the plutonium-calcium stability constant ratio to compare the relative effectiveness of possible chelating agents was extended by Catsch to include the competition for protons (85), which is very important in comparing ligands of different basicities. In addition to the equilibria between hydrogen, calcium, plutonium and the chelating agent, the hydrolysis of plutonium and the binding of plutonium to biological components are important. Although salicylic acid binds calcium very weakly ($K_{CaL} \sim 1$), its complexation of plutonium is too weak to promote excretion (72). Thus, while minimizing the complexation of calcium, the affinity of the chelating agent for plutonium at physiological pH must remain greater than that of biological components.

The relative affinity of polyaminocarboxylic acids for calcium is decreased by replacing carboxyl groups with hydroxyl groups. Thus, N,N-bis(2-hydroxyethyl)glycine was more effective in promoting plutonium excretion than NTA (86), and more effective than EDTA in increasing urinary excretion of cerium (82). The substitution of phosphate groups for carboxylate groups in EDTA increases the relative affinity for lanthanides and actinides (87). N,N'-Ethylenebis[N-phosphonomethyl]glycine removed more plutonium from rats than EDTA or trans-1,2-cyclohexanediaminetetraacetic acid (88). However, the completely phosphorylated analogue of EDTA was less efficient than EDTA at removing plutonium, probably because of steric complications (87). The longer bridge length of oxybis(ethylenenitrilo)tetraacetic acid, BAETA, allows the carboxylate groups to better encapsulate the plutonium and offers an additional binding site to account for its increased ability in plutonium removal compared to EDTA (89). Replacement of the ether oxygen in BAETA with sulfur considerably decreases its ability to remove plutonium (90).

The additional carboxylic acid group present in diethylenetriaminepentaacetic acid, DTPA, relative to EDTA increases the stability of its actinide complexes, while the complexation of calcium remains nearly constant (91). Thus, the octadentate DTPA was found to be superior to EDTA or zirconium, and slightly more effective than BAETA, in the removal of plutonium from animals (89,92-94). Prompt administration of a single dose of DTPA caused the excretion of 89% of the injected plutonium from pigs during the following six days, compared to 3% excreted by controls (95). DTPA injected in dogs ($\frac{1}{2}$ hour) or in mice (1 hour) following the plutonium promoted the excretion of 60-65% of the injected plutonium during 24 hours, compared to 2% and 6% excreted in untreated

dogs (96) and mice (97). A further delay in treatment results in less plutonium removal such that only 15% of the injected plutonium was excreted by beagles during the first day following DTPA treatment given two hours after the plutonium (98).

Delayed treatment with multiple doses of DTPA removes moderate amounts of plutonium from animals. Treatment of swine on five successive days two months after plutonium contamination removed 11-19% of the plutonium (95). The body burden of rats was reduced to 60% of the controls by treatment with DTPA administered on day 6, 8 and 11 after the plutonium injection (99). The largest decrease of plutonium was found in the soft tissues, but skeletal removal was more difficult, and the moderate amounts removed may not significantly reduce the number of bone tumors formed (59,100,101). Further details on the use of DTPA in removing internally deposited plutonium may be gained from other reviews (6,13,102,103).

Further increasing the number of carboxyl groups of a polyaminocarboxylic acid did not significantly increase plutonium removal. Triethylenetetraaminehexaacetic acid, TTHA, and DTPA were nearly equally efficient at plutonium removal (90,94,104-106), but TTHA was reported to be more toxic (106). Perhaps due to the formation of multinuclear complexes, the additional increase in the number of carboxyl groups in tetraethylenepentaaminehaptaacetic acid, TPHA, resulted in a chelating agent significantly poorer in plutonium removal than DTPA, but still more effective than EDTA (90,94). Although tri(2-aminoethyl)aminehexaacetic acid, TAAHA, and TTHA each have six carboxylic acid groups, TTHA is better able to encapsulate the metal ion and removes much more tho-

rium from rats than does TAAHA (94). As with EDTA, the complete phosphorylation of DTPA decreases its ability to remove plutonium (90).

The stability of the calcium complex of the naturally-occurring iron sequestering agent desferrioxamine B, DFOA, is 10^3, which is seven powers of 10 less than that of DTPA (107). Although the stability of its Fe(III) chelate is not much greater than that of DTPA, DFOA is significantly more efficient in iron decorporation, primarily due to its decreased affinity for calcium (108). If administered within 1 hour after an injection of plutonium, DFOA is more effective than DTPA in promoting the excretion of plutonium. However, the ability of DFOA to decorporate plutonium decreases more rapidly than DTPA as elapsed time between contamination and treatment increases; DFOA treatment begun 4-7 days after contamination was ineffective. Prompt treatment with DFOA reduced bone deposition to $\frac{1}{2}$ the amount in DTPA treated rats, while the metabolism of DFOA deposits more plutonium in the liver, and the low pH of the kidneys causes the release of more plutonium from the more basic hydroxamic acid groups of DFOA. Combined treatment of DFOA and DTPA removed the greatest amount of plutonium, as the plutonium freed by destruction of the Pu-DTPA complex in the liver and the kidney is recomplexed by DTPA (109-112). Rhodotoluric acid, 2,3-dihydroxybenzoyl-N-glycine and neoaspergillic acid, also naturally-occurring iron sequestering agents, removed less plutonium from hamsters than did DTPA (113).

The additive effect of DTPA and DFOA has prompted studies of the plutonium removal exhibited by other combinations of chelating agents. The simultaneous local administration of citric acid or 2,6-pyridinedicarboxylic acid in conjunction with DFOA or DTPA increased the amount of

plutonium nitrate absorbed and excreted from an intramuscular site compared to using DFOA or DTPA alone. Tartaric acid, 2,3-pyridinedicarboxylic acid, lactic acid or pyruvic acid had no effect when administered with DTPA or DFOA. Citric acid or 2,6-pyridinedicarboxylic acid when administered alone solubilized much of the plutonium from the intramuscular site, but the plutonium was redeposited in other body tissues instead of excreted (112,114). With the hope of enhancing systemic plutonium removal by the formation of mixed ligand complexes, catechol, salicylic acid and benzohydroxamic acid were administered simultaneously with DTPA, but the amount of plutonium removed did not increase (115). The extraordinary synergistic effect originally claimed for these compounds has been refuted by the author (116).

While DTPA is currently the reagent of choice in reducing the body burden of actinides (6), it is most effective in removing monomeric plutonium from the circulation system - thus preventing the deposition of plutonium in body tissues - which requires prompt treatment. DTPA removes very little hydrolyzed thorium or plutonium colloids or polymers (117). The decreasing efficacy of plutonium removal as the time between contamination and treatment increases indicates that the plutonium deposited in intracellular site is unavailable for complexation. Metabolic experiments show that intravenously injected EDTA or DTPA mix rapidly with extracellular fluid, but are unable to cross cell walls (118-120).

Very few cases of accidental plutonium contamination are likely to create a high blood level of plutonium. Only very small amounts of plutonium compounds are absorbed from the gastrointestinal tract. A maximum of 2% of ingested Pu(VI) citrate or 0.03% Pu(IV) citrate, and much

less of most other compounds, was absorbed by rats (121). This absorption was reduced by a factor of 10 by the oral administration of ion exchange resin (122). Only a small amount of an intramuscular deposit of plutonium nitrate was removed by an intravenous injection of DTPA, while a local application of DTPA one hour after contamination removed 80-90% of the plutonium. However, much less was removed by a local DTPA treatment applied 21 days after contamination, during which time the plutonium had formed insoluble, polymeric hydroxides (114). DTPA is totally ineffective in removing insoluble plutonium compounds as PuO_2 from intramuscular sites or from lungs. These conditions are best treated by surgical excision of contaminated tissue, lung lavage, or other methods of direct physical removal (103,123).

Protracted DTPA therapy removes plutonium as it is liberated from cells by natural processes or solubilized by body fluids from intramuscular or lung deposits. The slowness of these processes requires DTPA administration over long periods of time to remove significant quantities of plutonium. The usefulness of such therapy may be of little value in preventing cancer caused by the plutonium. Thus, there has been much emphasis applied to the development of a lipophillic chelating agent. The pentaethyl ester of DTPA surpassed DTPA at removing intracellular plutonium from the liver, but its enhanced toxicity prevents its use as a therapeutic agent (124). Several monoamides and monoesters of EDTA and DTPA were formed using long chain alkyl amines and alcohols, but none of these derivatives removed intracellular plutonium. However, the same group has reported a derivative of DTPA that removes significant quantities of plutonium from the liver of hamsters (113,20). A lipophilic derivative of DFOA, N-stearoyldesferrioxamine, was also

tested but it was no better than DTPA at removing intracellular plutonium (113). Two chelating antibiotics, vancomycin and cephalothin, were also ineffective at plutonium removal, either alone or in conjunction with DTPA (125).

The reticuloendothelial cells, which are especially concentrated in liver, spleen, lung, and bone marrow, rapidly remove colloids and polymers from the circulation system. Thus, it was hoped that an EDTA-cysteine copolymer would be phagocytized and release EDTA after degradation of the polymer within the cell. However, administration of the EDTA-cysteine copolymer did not increase the elimination of intracellular plutonium from rats (113). The administration of ^{14}C-EDTA encapsulated in lipid spherules, liposomes, resulted in a high intracellular concentration of chelating agent, such that 42% of the EDTA was distributed in the liver cells of mice. When administered three days after the plutonium, liposome encapsulated DTPA removed significantly more plutonium from the liver and the skeleton than did nonencapsulated DTPA. However, the majority of the plutonium was not removed. Although the amount of plutonium removed decreased, the relative advantage of the encapsulated form increased with an increasing delay in therapy (126,127). Encapsulation of DTPA did not increase its effectiveness when administered one day after the plutonium in rats and hamsters (128).

Glucan, a polysaccharide found in the cell walls of yeast, is also removed by the reticuloendothelial cells and its administration increases the amount of plutonium stored in the liver that is available for complexation and removal by DTPA. It is hypothesized that glucan

and plutonium are associated with lysosomes, the subcellular organells that are responsible for the digestion of foreign materials. The glucan is partially hydrolyzed which results in the osmotic swelling and dispersion of the polysaccharide and the stored plutonium (129-131). Similarly, up to 50% of the plutonium remaining in the liver after DTPA treatment has been removed by treatment with DTPA and copolymers of divinyl ether and maleic anhydride or of acrylic and itaconic acids (132,133). Neither glucan nor the synthetic polymers promote plutonium removal from bone and they increase the amount of plutonium in the spleen. In a similar manner, an additional 10% of americium was removed from the skeleton when an osteoporotic agent, which etches the bone surface, was used in conjunction with DTPA (134).

Despite its ability to remove much of the soluble plutonium present in body fluids, DTPA is not an exceptional chelating agent for tetravalent actinides. The formation constant of its plutonium complex is too low to displace hydroxides from the colloids and polymers of hydrolyzed plutonium or solubilize compounds such as PuO_2 at physiological pH. In addition, the inability of DTPA to completely coordinate the tetravalent actinides is shown by the easy formation of ternary complexes between Th(DTPA) and many bidentate ligands (135-137). The hydrolysis of Th(IV) and U(IV) DTPA complexes at pH near 8 is explained by the dissociation of H^+ from a coordinated water molecule (138-141). Further, the polyaminocarboxylic acids are toxic due to the indiscriminate complexation and removal of many metals of biological importance, primarily calcium and zinc (142-147). While use of $CaNa_3DTPA$ prevents hypocalcemia, prolonged therapy must be frequently interrupted to allow the replenishment of other essential metal ions (147,148). The zinc

salt of DTPA is less toxic, but the larger stability constant of the Zn-DTPA complex decreases the amount of plutonium removal. However, as the time between treatment and contamination increases the difference in the amount of plutonium removed by a single dose of either salt becomes insignificant. The lower toxicity of Zn-DTPA allows larger, more frequent doses, which may remove more plutonium during extended therapy than non-toxic amounts of Ca-DTPA (85,95,98,112,123). As exemplified by its pentaethyl ester, the toxicity of DTPA is increased by mobilization into cells where it can complex metal ions which are needed for cell functions. This casts serious doubts on the usefulness of DTPA derivatives to remove intracellular plutonium. Thus there is a need for the development of powerful chelating agents highly specific for tetravalent actinides, particularly Pu(IV).

IV. Synthetic Sequestering Agents Specific for Pu(IV)

Based on the similarities in the chemical and the biological transport and distribution properties of Pu(IV) and Fe(III) and the observation that microbes produce specific sequestering agents for Fe(III) that incorporate chelating groups such as hydroxamic acids and catechol, a series of sulfonated catechoylamide sequestering agents has been designed and synthesized for the specific role of complexing plutonium and other actinide(IV) ions. These synthetic macrochelates have been designed such that the chelating groups can form a cavity that gives eight-coordination about the metal and the dodecahedral geometry observed in the unconstrained actinide complexes composed of monomeric catechol ligands. The resulting compounds appear to bind tetravalent actinides strongly, while only weak complexation of trivalent and

divalent metals has been observed.

It is remarkable that there are many similarities between Pu(IV) and Fe(III) (Table 3). In fact, this similarity explains much of the biological hazard posed by plutonium, as described in the previous sections of this paper. These similarities range from the charge to ionic-radius ratios for Fe(III) and Pu(IV) (4.6 and 4.2 e/Å respectively), and their formation of highly insoluble hydroxides, to their similar transport properties in mammals. These similarities of Pu(IV) and Fe(III) suggested to us a biomimetic approach to the design of Pu(IV) sequestering agents modeled after the very efficient and highly specific iron sequestering agents, siderophores, that are produced by bacteria and other microorganisms to obtain Fe(III) from the environment (150-152).

The siderophores (Figure 1) typically contain hydroxamate or catecholate functional groups which are arranged to form an octahedral cavity the exact size of a ferric ion. Catechol, 2,3-dihydroxybenzene, and the hydroxamic acids, N-hydroxyamides, are very weak acids that ionize to form "hard" oxygen anions, which bind strongly to strong Lewis acids such as Fe(III) and Pu(IV). Complexation by these groups forms five-membered chelate rings, which substantially increases the stability compared to complexation by lone oxygen anions (153). That the hydroxamic acids strongly coordinate tetravalent actinides is supported by the formation constants presented in Table 4. Due to its higher charge and stronger basicity, the catecholate group forms stronger complexes with the tetravalent actinides than the hydroxamic acids. Thus our goal has been the incorporation of hydroxamate or catecholate functional groups

into multidentate chelating agents that specifically encapsulate tetravalent actinides.

The similarity between Fe(III) and the actinide(IV) ions ends with their coordination numbers. Because of the larger ionic radii of the actinide ions, their preferred coordination number found in complexes with bidentate chelating agents is eight. Occasionally higher coordination numbers are encountered with very small ligands or by the incorporation of a solvent molecule (162,163). Calculations of ligand-ligand repulsions indicate that either the square antiprism (D_{4d}) or the trigonal faced dodecahedron (D_{2d}) is the expected geometry for an eight coordinate complex. The coulombic energy differences between these polyhedra (Figure 2) is very small and the preferred geometry is largely determined by steric requirements and ligand field effects. Cubic coordination lies at higher energy, but may be somewhat stabilized if f-orbital interactions were important. Another important eight coordinate polyhedron, the bicapped trigonal prism (C_{2v}), corresponds to an energy minimum along the transformation pathway between the square antiprism and the dodecahedron (164-169). As seen in Table 5, all four of the above geometries are found in eight coordinate complexes of tetravalent actinides with bidentate ligands. However, the mmmm isomer of the trigonal faced dodecahedron is the most prevalent in the solid state.

Two fundamental questions in the design of an actinide-specific sequestering agent are the coordination number and geometry actually preferred by the metal with a given ligand. The structures determined for the actinide(IV) catecholates and hydroxamates, in which the steric constraints of a macrochelate are absent, indicate that the mmmm-isomer

of the dodecahedron (Figure 3) is preferred. For maximum stability and specificity this geometry should be achieved by the ligating groups of an optimized sequestering agent that encapsulates the tetravalent actinide in a cavity with a radius near 2.4 Å. An examination of molecular models showed that this could be accomplished by the attachment of four 2,3-dihydroxybenzoic acid groups to the nitrogens of a series of cyclic tetraamines via amide linkages as shown schematically in Figure 4. The size of the cavity formed is controlled by the ring size of the tetraazacycloalkane backbone such that a 16 membered ring appeared most promising for the actinides. Two tetra-catechol chelating agents were synthesized from 2,3-dihydroxybenzoic acid and 1,4,8,11-tetraazacyclotetradecane or 1,5,9,13-tetraazacyclohexadecane (188). Subsequent biological evaluation in mice showed that these compounds reduced the accumulation of plutonium in bone and liver. However, the actinide complex apparently dissociated at low pH and released the plutonium in the animals' kidneys (97). Titrimetric studies of these ligands showed that while they strongly complex tetravalent actinides, simple one-to-one complexes are not formed at or below neutral pH (189).

The performance of a ligand at low pH can be improved by increasing its acidity, thus reducing the competition with protons. The acidity of the catechol groups can be increased by the introduction of strongly electron withdrawing groups to the aromatic rings. A more acidic analog of the above ligands was prepared from 2,3-dihydroxy-5-nitrobenzoic acid and 1,4,8,11-tetraazacyclotetradecane. The nitro groups converted the ligand into an acutely active poison and substantially changed its solubility characteristics such that a large amount of plutonium was found in the soft tissues of the treated mice (97). In sharp contrast,

sulfonation at the 5 position of each 2,3-dihydroxybenzoyl group in the ligands prepared above improved their water solubility, stability to air oxidation and affinity for actinide(IV) ions at low pH (190). The increased acidity of the sulfonated derivatives prevented the deposition of plutonium in the kidneys of mice and promoted significant plutonium excretion without any appreciable toxic affects (97).

In order to examine the effect of greater stereochemical freedom, some tetra-2,3-dihydroxy-5-sulfobenzoyl derivatives of linear tetraamines have also been prepared (190). Maximum stability and specificity towards the actinides was obtained by optimizing the length of the methylene bridges between the amine functionalities. Butylene bridges between the nitrogens of the linear tetraamines gave better results in animal studies than ethylene or propylene bridges. The linear derivatives are significantly more effective than the cyclic catechoylamides in removing plutonium from mice (97). In accordance with the trans configuration of amine hydrogens found in the structure of 1,5,9,13-tetraazacyclohexadecane (191), adjacent catechoylamide groups are expected to lie on opposite sides of the macrocycle. While inversion about amides is well known, it may not be facile enough in these compounds for ready coordination of the actinide by all four catechol groups.

The sulfonated catechoylamide derivatives of linear tetraamines (Table 6) are the most promising actinide sequestering agents yet prepared. The 4,4,4- or 3,4,3-LICAMS were the most efficient of the catechoylamides tested. A single dose of either ligand administered one hour after the plutonium eliminated about 65% of the injected plutonium from mice (97). Perhaps more significant is the fact that in addition

to sequestering the plutonium from body fluids, skeletal plutonium was reduced to 22% of the control value at the time of ligand injection by 3,4,3-LICAMS. Monomeric N,N′-dimethyl-2,3-dihydroxy-5-sulfobenzamide, DiMeCAMS, and 2,3-dihydroxybenzoic acid removed very little if any plutonium and similar results were obtained for 2,3-dihydroxybenzoyl-N-glycine by Bulman and coworkers (113). This dramatic difference between the monomeric catechols and the synthetic tetracatechol compounds confirm our original design concept that a macrochelate would be effective biologically in Pu(IV) removal. Of the sulfonated catechoylamides only the 4,4,4-LICAMS showed any toxic effects in mice.

For comparison, DTPA, the most effective conventional chelating agent, was examined and found to remove 63% of the injected plutonium. However, the dose-response curve, Figure 6, shows that 3,4,3-LICAMS is much more effective than DTPA at lower doses - up to a two order of magnitude difference (192). This is a good indication that endogenous metals are not strongly bound by 3,4,3-LICAMS, while metals such as calcium and zinc bind strongly to DTPA, reducing the effective concentration of ligand available to complex plutonium. Thus a much larger amount of DTPA is required to achieve the same effect of a smaller quantity of 3,4,3-LICAMS, because of both a lower intrinsic affinity for actinide(IV) ions as well as a lower specificity. Of all the sequestering agents tested to date, 3,4,3-LICAMS, a derivative of the natural product spermine, is the most effective in plutonium removal at low dosages.

The greater efficacy of plutonium decorporation by 3,4,3-LICAMS compared to DTPA has also been observed in beagles (193). A single

intravenous injection of 3,4,3-LICAMS administered 30 minutes after the actinides removed about 86% of the injected plutonium, much better than the 70% removed by DTPA. Treatment with a combined dose of 3,4,3-LICAMS and DTPA removed very slightly more plutonium than 3,4,3-LICAMS alone. Serious toxic effects were seen in the kidneys of all dogs treated with 3,4,3-LICAMS, although the dose response curve of Figure 6 suggests that smaller doses should be nearly as effective and would avoid such toxic effects. In contrast, DTPA is much more effective in americium decorporation. This was expected since the affinity of catechol ligands for the larger and less acidic Ln(III) or An(III) ions is quite low. The measured ratio of the tetrakis(catecholato)Ce(IV)/Ce(III) formation constants of 10^{36} is an indication of the decreased relative affinity of 3,4,3-LICAMS for the trivalent versus tetravalent actinides (175).

V. Summary

We have briefly reviewed the biological hazards associated with the actinide elements. The most abundant transuranium element produced by both industrial nuclear power plants and nuclear weapons programs is plutonium. It is also potentially the most toxic - particularly due to its long-term hazard as a carcinogen if it is introduced into the body. This toxicity is due in large part to the chemical and biochemical similarities of Pu(IV) and Fe(III). Thus in mammals plutonium is transported and stored by the transport and storage systems for iron. This results in the concentration and long-term retention of an alpha-emitting radionuclide (^{239}Pu) at sites such as the bone marrow where cell division occurs at a high rate. The earliest attempts at removal of actinide contamination by chelation therapy were essentially heuris-

tic in that sequestering agents known to be effective at binding other elements were tried with plutonium.

The research described here is intended to be a rational approach that begins with the observation that since Fe(III) and Pu(IV) are so similar, and since microbes produce agents called siderophores that are extremely effective and selective sequestering agents for Fe(III), the construction of similar chelating agents for the actinides should be possible using the same chelating groups found in the siderophores. The incorporation of four such groups (primarily catechol and hydroxamic acid) results in multidentate chelating agents that can completely encapsulate the central actinide(IV) ion and achieve the eight-coordinate environment most favored by such ions. The continuing development and improvement of such sequestering agents has produced compounds which remove significant amounts of plutonium deposited in bone and which remove a greater fraction of the total body burden than any other chelation therapy developed to date.

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Table 1. A Comparison of the Acute Toxicity of Some Chemical Substances in Mice.[a,b]

Substance	$LD_{50/30}$, mmole/kg	Relative Toxicity
NaCl	44.52	1
$CaCl_2$	2.50	18
$ZrOCl_2$	0.96	46
$CrCl_3$	0.90	49
$ThCl_4$	0.89	50
$AlCl_3$	0.80	56
$Fe_2(SO_4)_3$	0.42	106
$Pb(acetate)_2$	0.37	120
$ZnCl_2$	0.18	247
TlCl	0.10	445
$CdSO_4$	0.033	1349
UO_2Cl_2	0.021	2145
$HgCl_2$	0.020	2283
^{239}Pu(IV)Citrate	0.0047 (rat) 0.0013 (dog)	9400
Strychnine	0.0015	30000
Botulinus Toxin A	3×10^{-9} mg/kg	

[a]Data for Pu from Refs. 4 and 5, organic poisons from Ref. 5, all others from Ref. 3.

[b]Note that this is to be distinguished from the chronic or long-term toxicity of such substances.

Table 2. Schematic Structures of Some Chelating Agents Used in Plutonium Therapy

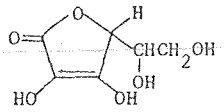
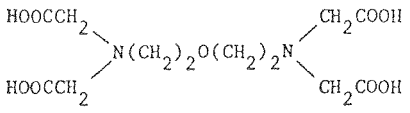
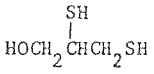
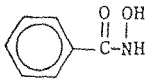
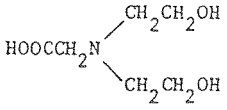
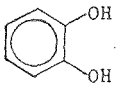
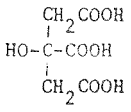
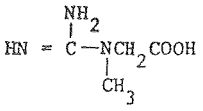
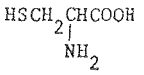
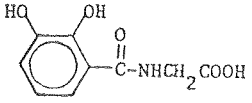
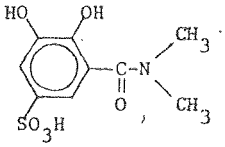
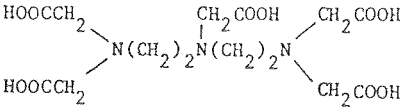
Ascorbic acid	
BAETA	
BAL	
Benzohydroxamic acid	
N,N-Bis(2-hydroxyethyl)glycine	
Catechol	
Citric acid	
Creatine	
Cysteine	
2,3-Dihydroxybenzoylglycine	
DiMeCAMS	
DTPA	

Table 2. (Continued)

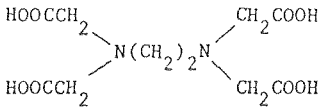
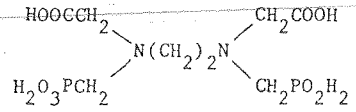
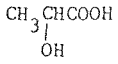
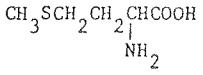
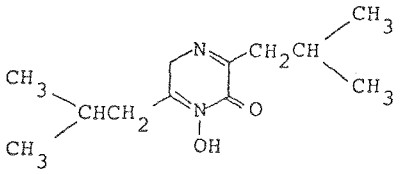
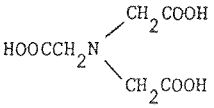
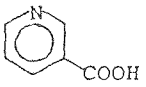
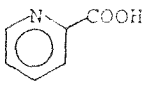
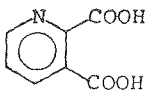
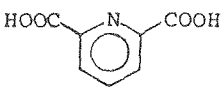
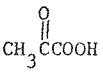
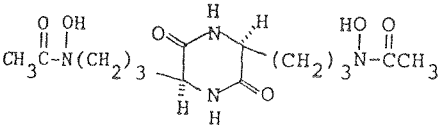
EDTA	
N,N'-Ethylene bis[N-phosphono-methyl]glycine	
Lactic acid	
Methionine	
Neoaspergillic acid	
NTA	
Nicotinic acid	
Picolinic acid	
2,3-Pyridinedicarboxylic acid	
2,6-Pyridinedicarboxylic acid	
Pyruvic acid	
Rhodotorulic acid	

Table 2. (Continued)

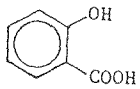
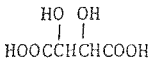
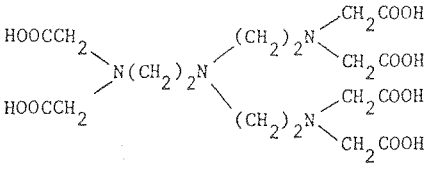
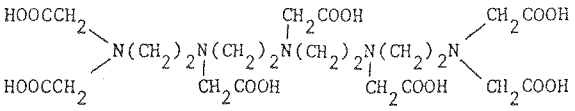
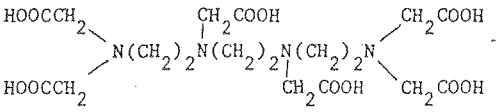
Salicylic acid	
Tartaric acid	
TAAHA	
TPHA	
TTHA	

Table 3. Similarities of Pu^{4+} and Fe^{3+}.

1)	$\frac{\text{Charge}}{\text{Ionic radius}^a}$	Pu^{4+}; $\frac{4}{0.96} = 4.2$	Fe^{3+}; $\frac{3}{0.65} = 4.6$
2)	$Fe(OH_3) \rightarrow Fe^{3+} + 3OH^-$		$K \approx 10^{-38}$ (10^{-13} per OH^{-1})
	$Fe^{3+} + H_2O \rightarrow Fe(OH)^{2+} + H^+$		$K = 0.0009$
	$Pu(OH_4) \rightarrow Pu^{4+} + 4OH^-$		$K \approx 10^{-55}$ (10^{-14} per OH^{-1})
	$Pu^{4+} + H_2O \rightarrow Pu(OH)^{3+} + H^+$		$K = 0.031$ (in $HClO_4$)
3)	Pu^{4+} is transported in the blood plasma of mammals as a complex of transferrin, the normal Fe^{3+} transport agent. The Pu^{4+} binds at the same site as Fe^{3+}.		

[a] Ref. 149.

Table 4. Formation Constants for Some Actinide(IV) Hydroxamates and Catecholates.

Metal	Temp, °C	log β_1	log β_2	log β_3	log β_4	Reference
Benzohydroxamic acid, Ph-C(O)-N(OH)-H						
U(IV)	25	9.89	18.00	26.32	32.94	154
Th(IV)	25	9.60	19.81	28.76		154
Pu(IV)	25	12.73				154
N-Phenylbenzohydroxamic acid, Ph-C(O)-N(OH)-Ph						
Th(IV)	20				37.70	155
Th(IV)	25				37.80	156
Th(IV)	30				37.76	157
Pu(IV)	22	11.50	21.95	31.81	41.35	158
N-Phenylcinnamohydroxamic acid, Ph-CH=CH-C(O)-N(OH)-Ph						
Th(IV)	20	12.76	24.70	35.72	45.72	159
Catechol						
Th(IV)	30	17.72				160
4-Nitrocatechol						
Th(IV)	25	14.96	27.78	36.71	40.61	161

[a] $\log\beta_n = [ML_n]/[M][L]^n$ for the reaction $M^{4+} + nL \rightarrow ML_n$ where L is the hydroxamate anion or the catecholate dianion.

Table 5. Geometry of Monomeric Eight-Coordinate Actinide Complexes with Bidentate Ligands.

Complex[b]	Metals	Idealized Geometry[a]	Ref.
α-M(IV)(acetylacetonate)$_4$	Th,U,Ce	$h_1h_1p_2p_2$-BTP	170,171
β-M(IV)(acetylacetonate)$_4$	Th,U,Np,Ce	ssss-SA	170,172
M(bipyridyl)$_4$	U	ssss-Cube	173
[M(IV)(catecholate)$_4$]$^{4+}$	Th,U,Ce	mmmm-DD	174,175
M(IV)(dibenzoylmethanate)$_4$	Th,U,Ce	mmmm-DD	176
M(IV)(N,N-diethyldithiocarbamate)$_4$	Th,U,Np,Pu	mmmm-DD	171,177
[M(III)(N,N-diethyldithiocarbamate)$_4$]$^-$	Np	mmmm-DD	178
M(IV)(diisobutrylmethanate)$_4$	U	BTP	179
M(IV)(hexafluoroacetonylpyrazolide)$_4$	Th,U	mmmm-DD	180
[M(III)(hexafluoroacetylacetonate)$_4$]$^-$	Am,Y,Eu	gggg-DD	181
M(IV)(N-isopropylpivalohydroxamate)$_4$	Th	ssss-Cube	182
M(IV)(N-isopropyl-3,3-dimethylbutanohydroxamate)$_4$	Th	mmmm-DD	182
M(IV)(salicylaldehydate)$_4$	Th,U	mmmm-DD	183
M(IV)(thenoyltrifluoroacetylacetonate)$_4$	Th,U,Pu,Ce	mmmm-DD	184,185

[a]BTP = bicapped trigonal prism, DD = trigonal faced dodecahedron, SA = square antiprism. The isomer notation is taken from references 168 and 169 and corresponds to the edges labelled in Figure 2.

[b]Thorium(trifluoroacetylacetonate)$_4$ was originally described as a 1111-SA (ref. 186), but a reinvestigation established the presence of a coordinated water molecule forming a nine-coordinate complex (ref. 187).

Table 6. Summary of Actinide Sequestering Properties of Tetrameric Catechoylamides.

Cyclic		
3,3,3,3-CYCAM	Mobilizes Pu but deposits it in kidneys	
3,2,3,2-CYCAM-NO_2	Very toxic	
3,3,3,3-CYCAMS, 2,3,3,3-CYCAMS	Sulfonation increases acidity and solubility, prevents Pu deposition in kidneys	
Linear		
2,3,2-LICAMS	Least effective of linear compounds	
3,3,3-LICAMS, 4,3,3-LICAMS	Longer chain length, slight improvement, still not very effective	
4,4,4-LICAMS	Slightly toxic	Longer central bridge gives optimum geometry
3,4,3-LICAMS	Derivative of spermine (a natural product)	

Less constrained linear structures are superior to corresponding cyclic compounds.

Figure Captions

Figure 1. Representative siderophores.

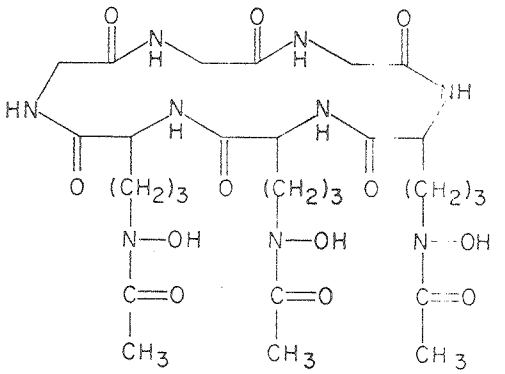
Figure 2. Eight-Coordinate polyhedra. The principal axes are vertical. Edge labels are taken from references 168 and 169.

Figure 3. The $[M(catechol)_4]^{4-}$ anion (M = Hf, Ce, Th, U) viewed along the mirror plane with the $\bar{4}$ axis vertical.

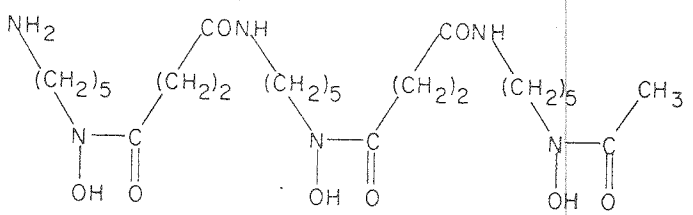
Figure 4. Schematic structure of the tetracatechol actinide sequestering agents from a biomimetic approach based on enterobactin.

Figure 5. Ceneral synthesis and structure of catechoylamides. The cyclic catechoylamides, in which R = $(CH_2)_p$ are abbreviated as n,m,p,m-CYCAM. The sulfonated and the analogous nitro derivatives are indicated by n,m,p,m-CYCAMS and n,m,p,m-CYCAM-NO_2 respectively. The linear sulfonated catechoylamides are abbreviated as m,n,m-LICAMS. A prefix is added to indicate terminal N substituents.

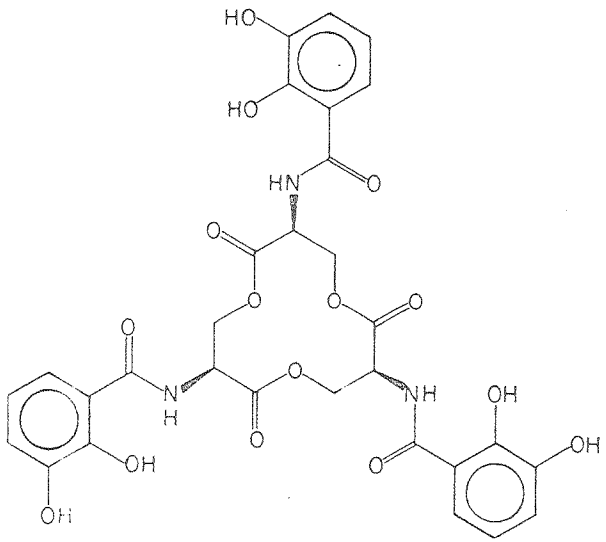
Figure 6. Dose response comparison between LICAMS and $CaNa_3DTPA$ for ^{238}Pu removal in mice.



Desferrichrome

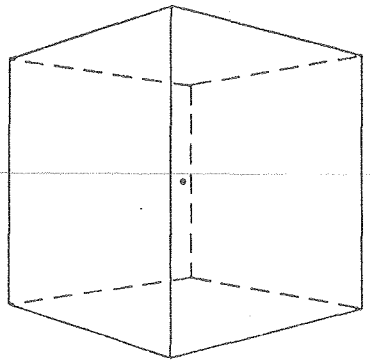


Desferrioxamine B

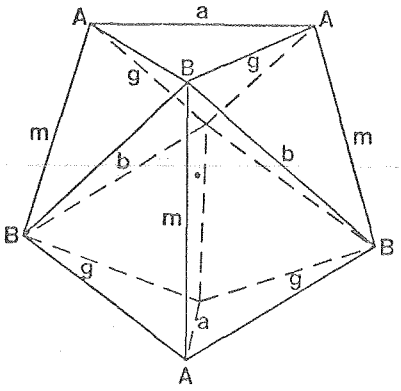


Enterobactin

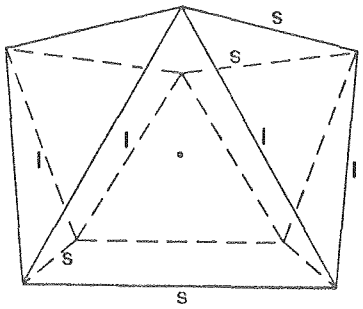
XBL 7910-4223



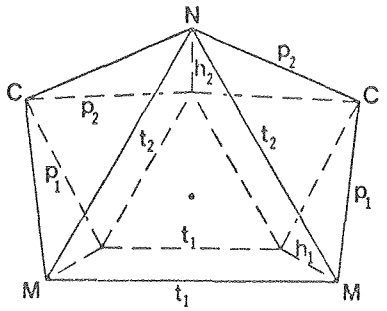
Cube
O_h



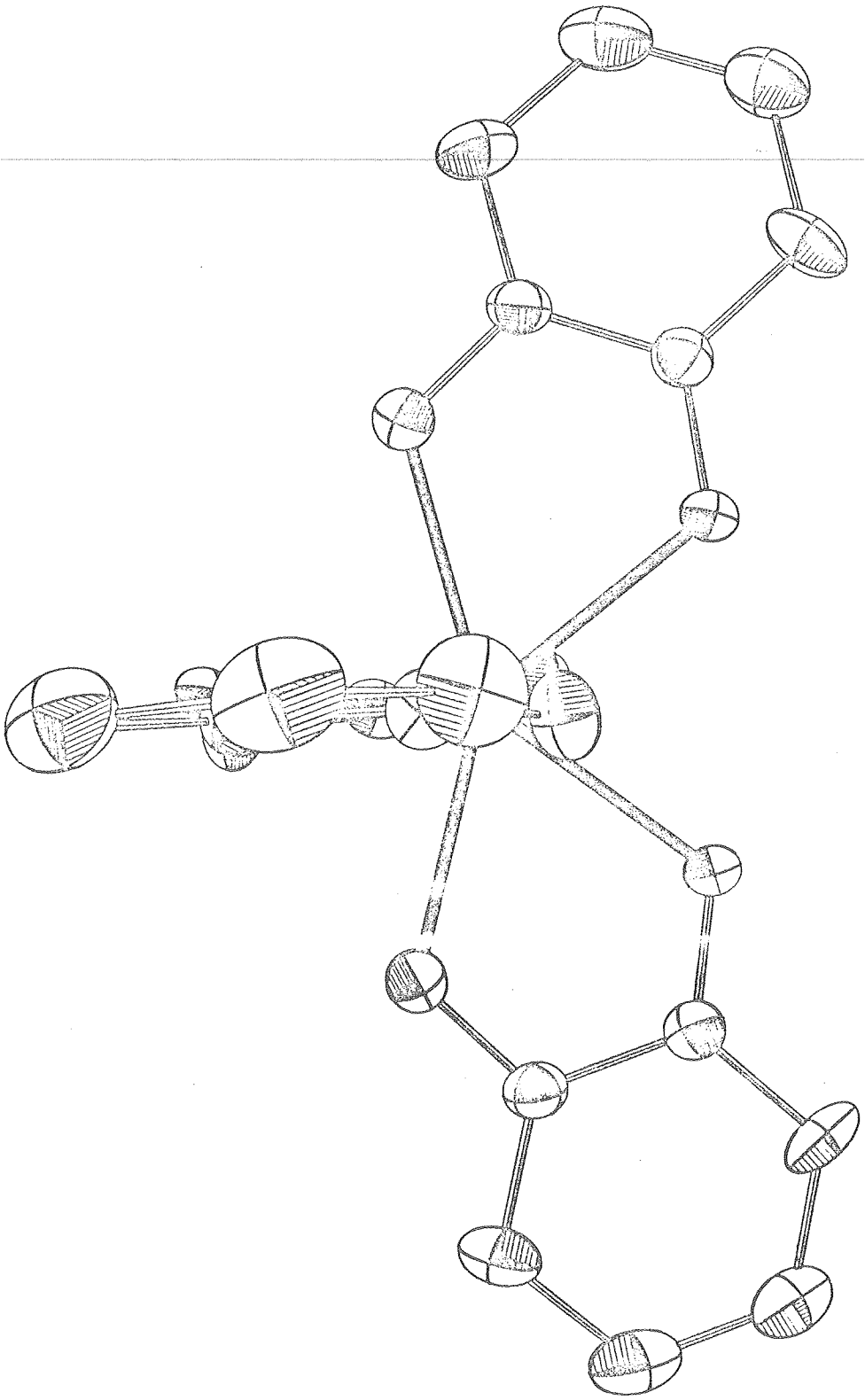
Dodecahedron
D_{2d}



Square Antiprism
D_{4d}



Bicapped Trigonal Prism
C_{2v}



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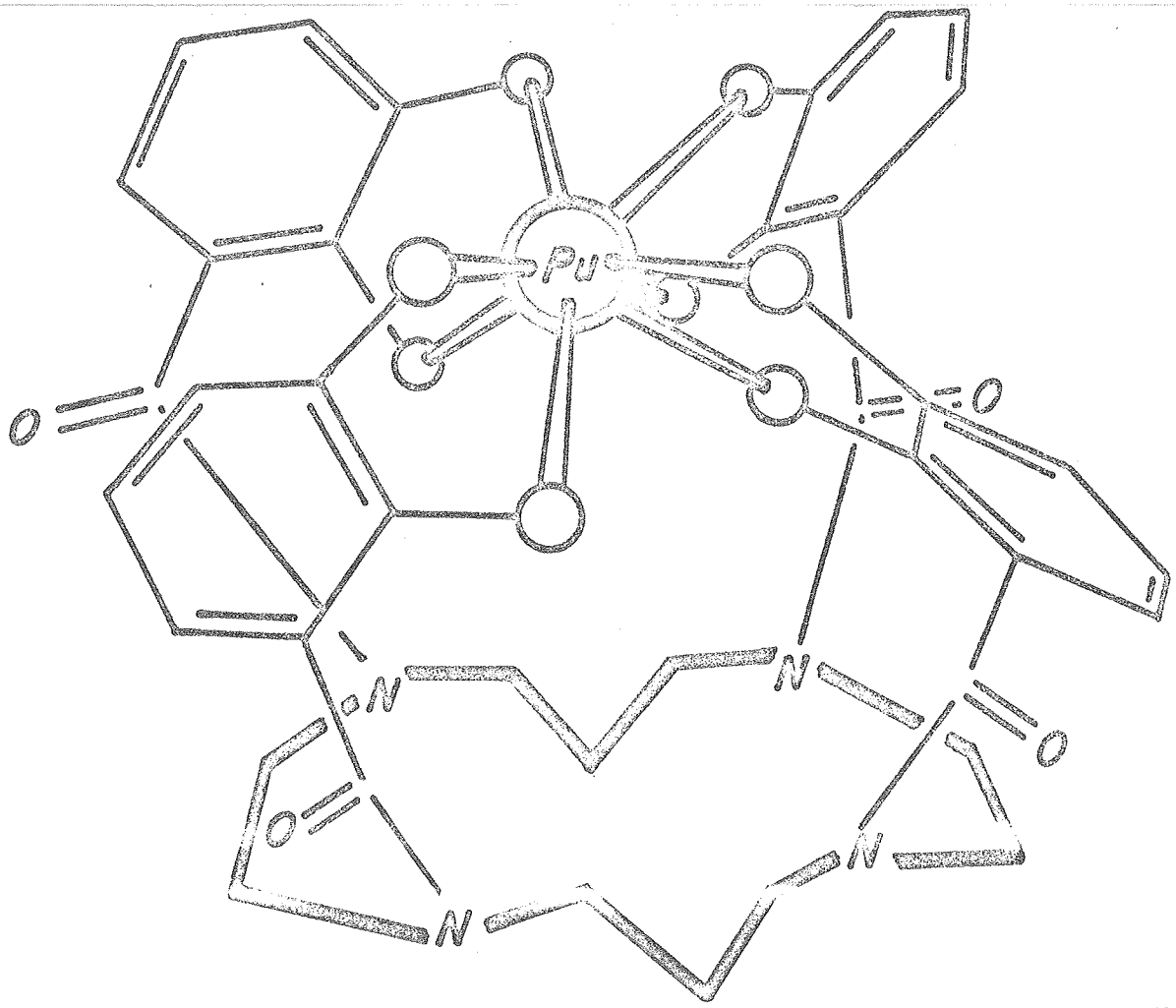

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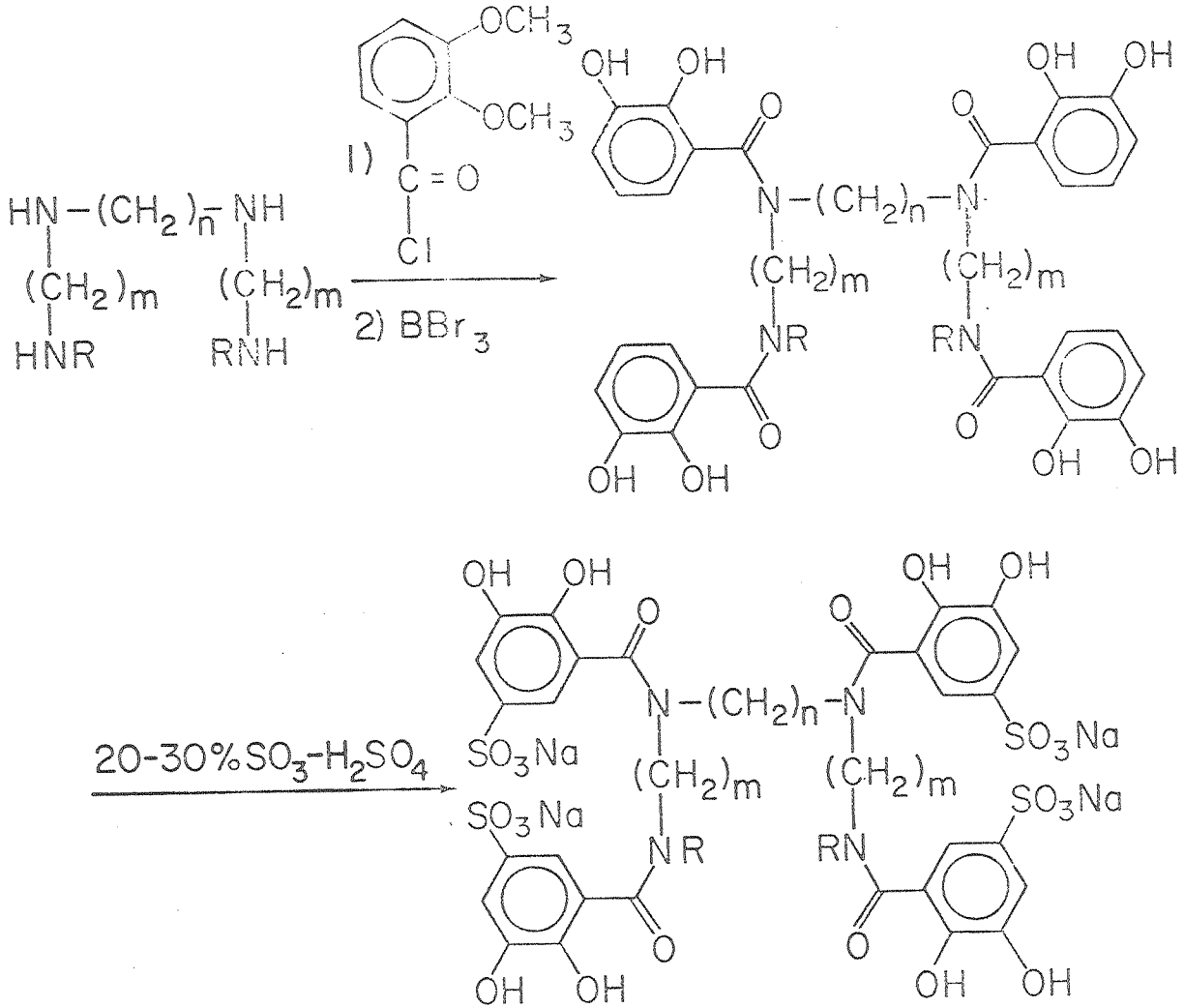

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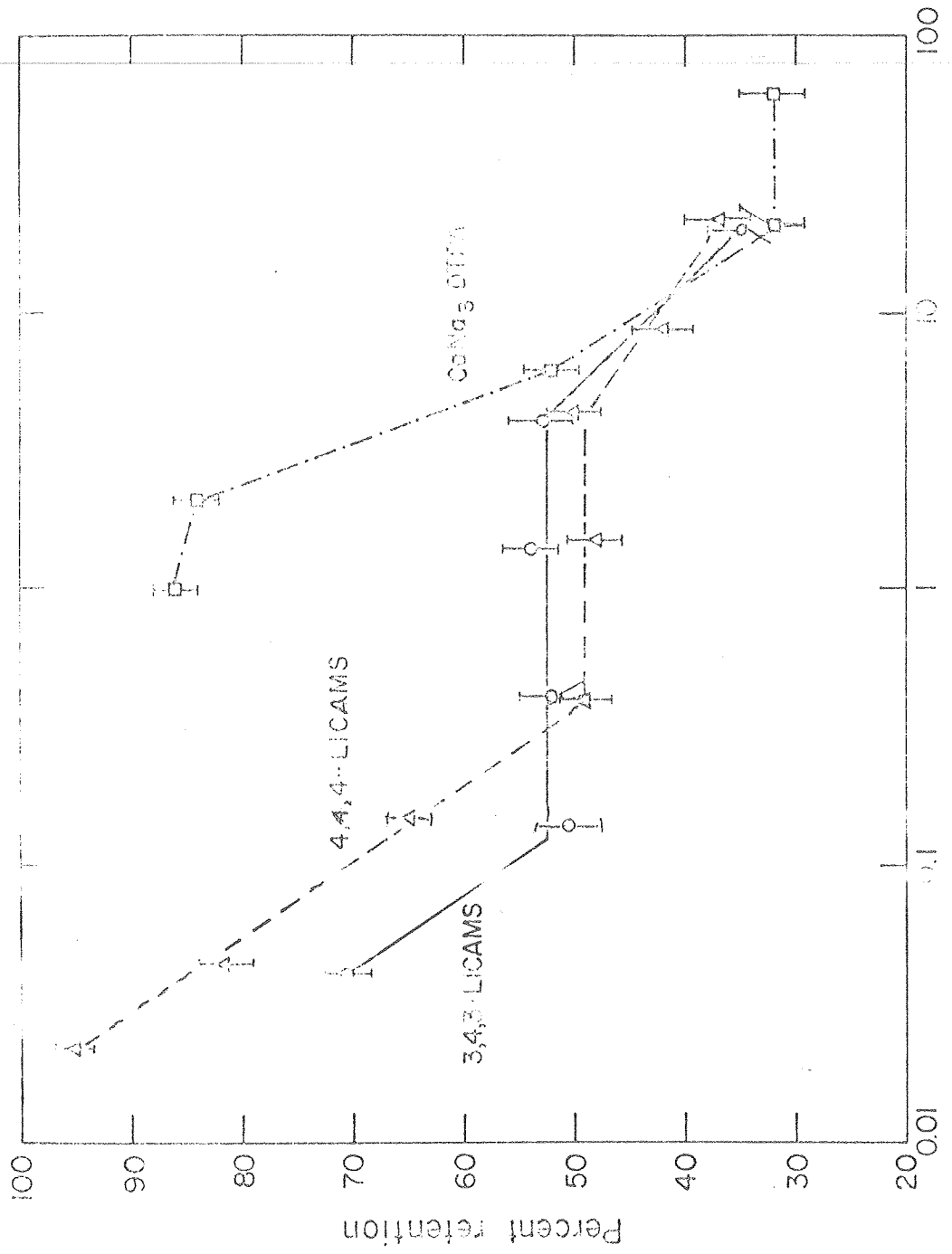

XBL 7910-4219